

ABSTRACT

Ectonucleoside triphosphate diphosphohydrolases [NTPDases; EC 3.6.1.5] constitute a family of enzymes which are involved in the metabolism of extracellular nucleotides, catalysing the hydrolysis of the gamma and beta phosphate bonds of triphospho- and diphosphonucleosides (whereas 5' nucleotidases [EC 3.1.3.5] catalyse the hydrolysis of alpha phosphate bond of monophosphonucleosides). These extracellular nucleotides interact with endothelial, epithelial and smooth muscle cells, as well as blood cells and lymphoid cells, to influence the different physiological systems of vertebrates. Since these ecto-nucleotidases alter the extracellular concentrations of nucleotides these enzymes modulate their physiological effects, including, for example, platelet aggregation, heart function, control of vascular tone and inflammation reactions, electrolyte secretion and gastrointestinal motility, neurotransmission both in central and peripheral nervous systems, as well as other effects in other physiological systems. This invention provides C8 substituted purine nucleotide analogues, such as ATP analogues, and further provides their use as inhibitors of NTPDases and thereby as tools to modulate the conversion of nucleotides into nucleoside derivatives, and thus modulate the levels of these compounds. Such modulation further provides for the modulation of the activity and function of many processes which are affected by these compounds.